interview included the adequacy of the disclosure with regard with to providing a functional α_1 subunit and the practical utility of T-type receptors of which this α_1 subunit is a part.

In accordance with the Examiner's position that the rejections are based upon Office policy as opposed to an evaluation of the claims in accordance with the requirements of the statute, the scheduling of an interview with Examiners Basi and Egler and Specialist Stanton on April 22 is much appreciated. Nevertheless, careful consideration has been given to the grounds for rejection, and the following discussion is offered in response. Reconsideration is respectfully requested.

REMARKS

Applicants appreciate acknowledgement of the amendment filed 23 July 2001 and of the declaration filed on the same day.

The Invention

The invention is directed to methods to identify compounds which behave as agonists or antagonists of T-type calcium channels. The method requires recombinant production of the α_1 subunit of such receptors and display of these subunits on the cell surface. Having a displayed α_1 subunit, compounds can be tested for their ability to agonize or antagonize the channel. The compounds thus identified can be used to regulate the activity of T-type calcium ion channels in subjects where the activity is abnormal.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 25-27 and 31-33 were rejected as indefinite. As to claims 25-27, the Office states that a method claim must contain a preamble, method steps, and a conclusion. It appears to applicants that claim 25 meets these requirements. There is a preamble (A method to identify a compound that behaves as an agonist); two method steps (contacting recombinant cells expressing an α_1 subunit of a T-type channel and determining the ability of the compound to activate the subunit) and there is a conclusion (a compound that activates the α_1 subunit is

identified as an agonist). The conclusion is symmetric with the preamble. It is not clear to applicants what further explanation is expected. Certainly this is the case for claims 26-27 where specific methods to measure the activity of the channel are identified.

The function of the claims is to define the metes and bounds of the invention, not to teach how the invention is to be performed. That is the function of the specification. The nature of the steps is described in the specification, for example, at page 17, lines 7-24. This leaves aside the fact that those of ordinary skill in the art understand anyway that there is a variety of methods whereby the activity of a T-type calcium channel could be measured and practitioners in the art would know how to do this without any instruction at all from the applicant. Standard voltage clamp methods are available, as well as the fluorescent dye method mentioned in claim 27.

With respect to claim 31, again applicants are puzzled by the position of the Office. This claim contains a clear preamble, steps, and an explanation of how agonists and antagonists are identified. It should be clear from the claim that the purpose is not to distinguish antagonists from agonists, but rather to identify a class of compounds which would exhibit one of those two activities.

With respect to claim 32, the claim is not required to teach how to carry out the analysis, but rather to set the metes and bounds of the invention. Competitive binding assays are well known, as is the method of conducting equilibrium binding measurements using labeled compounds.

Accordingly, this basis for rejection may properly be withdrawn.

Applicants do not understand the paragraph on page 3 of the Office action, beginning at line 5, which does not appear to address the rejection under 35 U.S.C. § 112, paragraph 2. It is assumed that it is intended that this paragraph be placed under the rejection on the following page with regard to 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph. It will be addressed in that context.

The Rejections Under 35 U.S.C. §§ 101 and 112, First Paragraph

This rejection is grounded almost entirely on an asserted lack of utility.

Utility of the T-Type Receptor Represented by the Disclosed α_1 Subunit

The first aspect of this rejection appears to reside in a blanket statement that there is no evidence in the specification or in the art that screening test for agonist or antagonist of the T-type receptor has any practical utility; including the question of whether the α_1 subunit itself can serve as a surrogate for the T-type receptor.

Turning first to the paragraph on page 3 of the Office action, respectfully, the function of the novel α subunits α_{1G}, α_{1H} and α_{1I} is indeed described in the specification. First, the application states clearly on page 5, at line 1, that the α_1 subunits alone can form functional calcium channels. Although the properties of these channels may be modulated by coexpression with other subunits, the α_1 subunits alone are functional. The specification also clearly states on page 7 that the α_{1G}, α_{1H} and α_{1I} subunits are those of T-type calcium channels. Since these subunits alone are functional and since they are subunits of the T-type calcium channel, they can clearly serve as surrogates for the T-type calcium channels in assessing agonist and antagonist activity and the agonists/antagonists are useful in treating conditions associated with abnormal function of T-type channels.

As the Office admits in the bridging sentence on pages 5-6, the specification does state specific conditions where abnormal T-type channel function needs to be corrected. The Office also acknowledges the description, which was supported by citations to the literature, of conditions associated with abnormal T-type function in Dr. Snutch's declaration.

The declaration of Dr. Snutch submitted and of record as of July 2001, states clearly in paragraph 2 that abnormal T-type activity is associated with cardiac conditions, including pacemaker activity, cardiac hypertrophy, and hypertension and with neurological diseases such as epilepsy; and indeed with infertility. Documents published in the art prior to the application date are cited in support of this. The Office has offered no evidence or rationale to doubt that

this nexus exists. Applicants believe it is incumbent on the Office to accept the sworn testimony of Dr. Snutch, especially when it is supported by publications from peer-reviewed journals, unless some reason is provided to doubt this. Applicants find nothing in the record that questions Dr. Snutch's statements. All the Office appears to say is that utilities associated with treating these conditions are not substantial or specific.

Applicants are unable to see how the Office can assert that these utilities are not substantial or specific. Is not treatment of epilepsy substantial and specific? Is not cardiac hypertrophy substantial and specific? Is not infertility substantial and specific?

The Office goes on to state that the specification does not disclose any disease states treatable by the polynucleotides or polypeptides of the invention; clearly this is irrelevant as it is agonists and antagonists for the calcium ion channels that would be the agents for treatment. And, the possibility that the art may not yet have found any useful substances to block T-channel ion activities or to activate it is irrelevant to the present claims as it is the very purpose of the methods of these claims to find such compounds.

How can the Office state that the disclosed utilities are methods of treating "unspecified, undisclosed diseases or conditions" when the claims are not directed to treating anything, but rather to using the recombinantly produced α_1 subunits of the invention as screening tools to find such agents for treatment.

The citation of *Brenner v. Manson* is noted; applicants point out that in that case, the claims were directed to a method to synthesize a steroid whose function was undisclosed and unknown. In the present case, the function of the α_1 subunits is disclosed - it is useful as a tool, not to find out what it does, but in the identification of compounds useful in treating diseases and conditions which the Office itself sets forth in its Office action.

Applicants wish to call the attention of the Office to U.S. patent 6,358,706 issued 19 March 2002 based on an application filed 26 October 1999. The claims in this patent are directed to an isolated and purified DNA molecule that encodes a human calcium channel α_{1G}

subunit protein. Apparently, the Office found the α_{1G} subunit of the human calcium ion channel cloned by that patentee useful. The uses ascribed to substances which interact with that channel are similar to those here, as stated in column 6 of the '706 patent. "The recombinant protein is useful to identify modulators of the α_{1G} calcium channel. Modulators identified in the assays disclosed are useful as therapeutic agents..." (see lines 32-54).

Also of interest is U.S. patent 6,309,858 which issued on an application field September 23, 1999, which claimed priority from a provisional application filed September 29, 1998. Claims were issued in that case to polynucleotides encoding α_1 subunits of T-type receptors in humans. Again, the utility for these products is as a screen for agonists and antagonists to treat the very same conditions applicants have discussed.

If it is "Office policy" that precludes acknowledgement of utility herein, it is respectfully submitted that the Office policy is not being equitably applied.

In the interview, when the question of the utility disclosed in the '706 patent was raised, the Examiner pointed out that the '706 applicants had demonstrated that the α_{1G} subunit described therein binds to mibefradil. Applicants fail to see the relevance of this information. It is never stated what implications if any such binding has for treating disease. There is no showing that the binding of mibefradil to the specific α_{1G} subunit disclosed is specific. Indeed, it is made clear that a different compound which binds to this subunit, in NPPB, also blocks chloride channels (see column 27, line 64-65).

In the discussion at the interview, the Examiner took the position that if there is a known agonist for a calcium ion channel, this automatically shows that the calcium ion channel must be useful. Applicants are unable to follow this logic. If the compound which binds is not a known pharmaceutical, there is no more logical path to conclude that blockage of the relevant receptor will be associated with a unwanted disease condition than there is in the present application. If the compound is a known pharmaceutical with a known target treatment, it still does not follow that it is the interaction with the T-type calcium channel which is the mechanism for its effect

with regard to the disease condition. The interaction with the calcium ion channel may simply be a side effect of the drug.

So the foregoing statement holds. There is no more evidence of utility in the '706 patent than there is in the present application; the utilities set forth in the '706 patent are rightly judged to support patentability of the recombinant materials for production of this subunit.

The Examiner also indicated that the assertion of more than one possible disease target undermines the specificity of the utility. Applicants call the attention of the Office to column 17 of the '706 patent, beginning at line 20 and extending to column 18, line 5.

Applicants have Provided the Art with, and are Claiming, a Functional α_1 Subunit of a T-type Calcium ion Channel

As to the objection that the invention is not useful "especially when the complete sequence of the claimed invention is not known," this is addressed by the declaration of Dr. Snutch of record in the parent application herein. As disclosed in that declaration, SEQ. ID. NO: 18 provides sufficient amino acid sequence to permit one of ordinary skill to provide a functional α_1 type subunit. A copy of this declaration is attached as Exhibit A.

In response to the request made at the interview that Applicants point out the specific portions of the declaration of Dr. Snutch, to which response is requested, Applicants first note that this issue was not raised in the previous Office Action, and so the previous response had not included a copy of this declaration as an exhibit. However, with respect to the declaration as now included, it will be noted that Dr. Snutch goes into considerable detail to explain the fact that the disclosure of SEQ. ID. NO: 18 is sufficient to describe to the ordinarily skilled artisan a functional α_1 subunit. As Dr. Snutch states in paragraph 9, based on the information set forth in SEQ. ID. NO: 18, one of ordinary skill in the art would understand that it encodes about 85% of the functional T-type calcium ion channel and would be able to envision an amino acid sequence representing the missing C terminal portion based on homology to the three domains encoded by the disclosed sequence. Thus the practitioner would be just as able to construct an expression

system containing a nucleotide sequence encoding a functional subunit based on applicatants' disclosure as would be possible from the disclosure of a full-length clone. In other words, sufficient information is provided to the art that without any experimentation at all, a functional T-type subunit can be obtained. Dr. Snutch is not just making this up, the previous paragraphs of the declaration provided a detailed explanation of why it is that no further invention is required to make a functional nucleotide sequence from the information disclosed.

For the reasons stated above, it is believed that the Office has not made out a *prima facie* case of lack of utility.

The Section 112 Aspects

With respect to the additional aspects of this rejection under 35 U.S.C. § 112, first paragraph, that the "general structural attributes definitive of α_1 subunit for T-type calcium channels are not taught in the specification or known in the art," it is respectfully submitted that this is not the case. This is also addressed in detail in Dr. Snutch's declaration; as stated therein, in addition to there being sufficient sequence provided to obtain a functional subunit, the features of such a subunit are described in detail in Dr. Snutch's declaration based on the art-known characteristics of α_1 subunits of calcium ion channels in general. See, for example, paragraph 2, which describes the generic characteristics of calcium ion channels and paragraph 6, which outlines the characteristic amino acids for the alternative known channels showing there is consistency in amino acids sequence among the structural domains, thus providing evidence as set forth in paragraph 8 that the nature of the amino acid sequence and domain IV can be surmised from the amino acid sequence of domain III. Accordingly, this basis for rejection may also be withdrawn.

CONCLUSION

Applicants appreciate that the claims are not rejected over the art. The rejections under 35 U.S.C. §§ 112/101 are believed misplaced for the reasons stated above and applicants request that claims 25-33 be passed to issued forthwith.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 381092000720.

Respectfully submitted,

Dated: April 10 , 2002

By: Kate H. Murashige

Kate H. Murashige
Registration No. 29,959

Morrison & Foerster LLP
3811 Valley Centre Drive
Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5112
Facsimile: (858) 720-5125

PATENT
Docket No. 381092000700

CERTIFICATE OF MAILING BY "FIRST CLASS MAIL

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on June 4, 2001.

Jami M Procopio

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Terry P. Snutch, *et al.*

Serial No.: 09/030,482

Filing Date: 25 February 1998

For: NOVEL HUMAN CALCIUM CHANNELS AND RELATED PROBES, CELL LINES AND METHODS

Examiner: Nirmal S. Basi

Group Art Unit: 1646

EXPEDITED PROCEDURE -- EXAMINING GROUP 1646

DECLARATION OF DR. TERRANCE SNUTCH

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Terrance Snutch, declare as follows:

1. I am a co-inventor of the subject matter claimed in the above-referenced application and have been practicing in the field of molecular biology, and specifically in the field of ion channels, for over 15 years. A copy of my *curriculum vitae* is attached hereto as Exhibit A. I have published many papers on the structure and function of calcium channels and am considered one of the leading researchers in this field.

2. The nucleotide sequence set forth as SEQ. ID. NO: 18 encodes about 85% of the total amino acid sequence, starting at the exact N-terminus, of a member of a family of voltage-gated ion channels that contain four homologous structural domains (domains I, II, III and IV). All of the identified members of this four-domain class of ions channels are either voltage-gated

calcium or sodium ion channels. In each case, each of the four homologous domains contains structural elements necessary for channel function. Each contains six transmembrane segments including a transmembrane segment called the S4 region that acts as the voltage sensor of the channel. Also contained in each homologous domain is a region called the P-loop or Pore region that contains specific amino acid residues responsible for ion selectivity. Voltage-gated sodium and calcium channels can easily be distinguished from each other based upon their overall degree of sequence conservation and by the specific amino acid residues that constitute the Pore region responsible for ion flux (see below).

3. I have concluded that SEQ. ID. NO: 18 encodes virtually the entire amino acid sequence of a major branch of the calcium channel family that represents a T-type channel. The calcium channel family and the evolutionary relationships between its members are shown in Figure 1. The construction of the family is based on sequence homology in the genes encoding the various members. As seen in Figure 1, a closely related branch of the family is represented by several types designated P/Q, N and R; this major branch is more distantly related to another branch which is represented by various L-type channels. The nucleotide sequence set forth in the present invention as SEQ. ID. NO: 18 has characteristics which place it in this general family, but it is relatively distantly related to the two branches represented by the α_1 subunits A, B, E and α_1 subunits S, C and D. My conclusion that Figure 1 represents an accurate characterization of SEQ. ID. NO: 18 is based on the reasoning set forth in paragraphs 4-6 below.

4. Over the past 30 years native calcium channels have been classified into high-threshold (L-type, N-type, P/Q-type and R-type) or low threshold subtypes (T-type), as illustrated in Figure 1. The placement of the high-voltage types is based on evolutionary analysis of already cloned calcium channels. This shows that the P/Q-type, N-type and R-type calcium channel α_1 subunits constitute one branch of calcium channels while the L-type subunits α_1C, α_1D and α_1S constitute a second evolutionary branch. The only class of calcium channel not accounted for is the third branch which would thus include the T-type. Comparison of SEQ. ID. NO: 18 deduced amino acid with that of the other α_1 subunits clearly indicates that it forms a third evolutionary class of calcium channel, which based upon physiological and pharmacological criteria must represent the T-type channel.

5. Examination of the Pore region of SEQ. ID. NO: 18 compared to the high threshold calcium channels and also sodium channels indicates that SEQ. ID. NO: 18 encodes a novel type

of calcium channel. In all high threshold calcium channels, the pore region of each domain (I, II, III, and IV) contains a glutamate residue (E) that is responsible for the selective flux of calcium through the channel (Yang, *et al.*, 1993, "Molecular Determinants of Ca Selectivity and Ion Permeation in L-type Ca Channels," *Nature* 366:158-161). In contrast, sodium channels possess other amino acids in the analogous positions (domain I = aspartate (D), domain II = glutamate (E), domain III = lysine (K). Mutation of the domain III lysine (K) of sodium channels to the corresponding glutamate (E) found in the high threshold calcium channels results in the flux of calcium and indicates that the domain III pore region is critical to defining ion flux (Heinemann, *et al.*, 1992, "Calcium Channel Characteristics Conferred on the Sodium Channel by Single Mutations," *Nature* 356:441-443). It is known from the behavior of the calcium channels whose genes had not yet been cloned that these "T-type" calcium channels possess distinct permeation properties compared to high-threshold calcium channels. In general, while high-threshold calcium channels flux barium at a higher rate than calcium, T-type channels flux calcium at a similar or higher rate than that for barium (for review, see Huguenard, 1996, "Low-Threshold Calcium Currents in the Central Nervous System Neurons" *Annu. Rev. Physiol.* 58:329-348). Examination of the Pore region of SEQ. ID. NO: 18 shows that in domain III it contains the substitution of an aspartate residue (D) for the glutamate residue (E) that is absolutely conserved in all of the high threshold calcium channels. A comparison of the relevant positions in the Pore regions of domains I, II and III of the known calcium channels, the sodium channel, and SEQ. ID. NO: 18 is shown in Figure 2. Since the domain III glutamate (E) residue of the high threshold calcium channels is critical for ion flux (Yang, *et al.*, 1993, *supra*), one can conclude that the substitution of D for E in SEQ. ID. NO: 18 contributes to the unique permeation properties of the T-type channel.

6. The intracellular linker region separating domains I and II of all high threshold calcium channels contains a high-affinity binding site for the calcium channel β subunit. The consensus β subunit binding site found in the N-type, P/Q-type, L-type and R-type channels is: QQ-E—L-GY—WI---E and is a defining characteristic of high threshold calcium channels (Pragnell, *et al.*, 1994 "Calcium Channel β-Subunit Binds to a Conserved Motif in the I-II Cytoplasmic Linker of the α_1 Subunit," *Nature* 368:67-70). It is known that T-type calcium channels do not contain or bind to the β subunit of high threshold calcium channels. The amino

acid sequence encoded by SEQ. ID. NO: 18 does not possess the consensus β subunit binding sequence. This is consistent with SEQ. ID. NO: 18 encoding a T-type calcium channel.

7. For the reasons set forth in paragraphs 4-6, I am certain that SEQ. ID. NO: 18 encodes a T-type calcium ion channel α_1 subunit. To summarize, as set forth in paragraph 4, a comparison of the deduced amino acid sequence in SEQ. ID. NO: 18 with that of other known four-domain voltage gated channels shows that it is relatively distantly related from the calcium channels whose genes have already been cloned and amino acid sequences deduced and thus belongs to the low-threshold subtype (T-type) which had not heretofore been cloned; paragraph 5 demonstrates that the critical amino acids in the Pore region verify that it is a calcium ion channel rather than a sodium ion channel and that it is distinct from the already cloned high-threshold channels, and paragraph 6 demonstrates that as expected, the deduced amino acid sequence lacks a β subunit binding sequence. The coding sequence is not entirely complete (approximately 85%), but it is sufficient both to (1) verify its nature as encoding a T-type calcium ion channel subunit and (2) to provide sufficient information to permit supplementation with additional nucleotide sequence to encode a functional T-type channel without retrieving a full length clone.

8. SEQ. ID. NO: 18 contains an ATG start codon that precedes three complete homologous structural domains I, II and III, and up to the S1 transmembrane segment of domain IV. Each of the domains I through III possesses an intact voltage sensor segment (S4) as well as a complete Pore region. Since structural domains II, III and IV result from the evolutionary duplication of domain I, SEQ. ID. NO: 18 contains sufficient information to construct a complete domain IV and thus a functional T-type calcium channel α_1 subunit. The nature of the amino acid sequence in domain IV can be surmised from the amino acid sequence of domain III. Of course, means to construct a nucleotide sequence extending the nucleotide sequence of SEQ. ID. NO: 18 to include a nucleotide sequence encoding this deduced amino acid sequence are routine.

9. In summary, one of ordinary skill in the art given the information set forth in SEQ. ID. NO: 18

(a) would understand that it encodes about 85% of a functional T-type calcium channel α_1 subunit starting at the N-terminus,

(b) would be able to design an amino acid sequence representing the missing C-terminal portion based on homology to the three domains encoded by SEQ. ID. NO: 18, and

(c) would be able to construct an expression system containing a nucleotide sequence encoding a functional T-type calcium ion channel α_1 subunit without obtaining a full length clone.

10. In addition to the foregoing demonstration that the application discloses the essential features of a T-type calcium channel, I further provide information regarding the nexus between all T-type calcium channels and identified conditions which can be treated with compounds that interact with T-type calcium channels. There are several T-type calcium channels found in a single individual which vary slightly in structure and demonstrably in terms of their distribution among various tissues. The particular T-type calcium channel involved in a particular condition may depend on its tissue distribution; for instance, T-type channels found in the neuronal system are associated with epilepsy and neurological diseases in general where spastic convulsions are involved. However, it is not necessary to understand which particular T-type calcium channel is being used in a screen for compounds that would be useful in treating, for example, these convulsive conditions because of the similarity in the binding specificity of all T-type channels. In very simple terms, compounds which are found to inhibit the activity of neuronal T-type channels will also inhibit the activity of T-type channels found in other tissues. Thus, any arbitrarily chosen T-type channel could be expressed in a cell line for use in screening assays to identify antagonists and the antagonists would be useful in treating the conditions associated with any T-type channel. As noted in the accompanying response, abnormal T-type activity is associated with a number of cardiac conditions, with hypertension, with neurological diseases involving spastic convulsions, and with impaired fertility. An antagonist identified with regard to any T-type channel would be useful in all of these conditions.

11. The pattern of similar binding activity among all T-type channels can be analogized to such a pattern among L-type channels. All of the T-type channels have similar behaviors in that they activate at low membrane potential, have small single channel conductance, have negative steady state inactivation properties, and contribute to spike firing patterns and rhythmic bursting processes. Analogous to the T-type channel another type of channel linked by similar behaviors is the L-type. There are several α_1 subunits associated with various L-type channels - *i.e.*, α_{1S}, α_{1C}, and α_{1D} and each is encoded by a distinct gene and exhibits a distinct distribution

pattern. For example, α_{1S} is in skeletal muscle; α_{1C} is in neurons and cardiac and smooth muscle; and α_{1D} is found in neurons and endocrine cells. They can be discriminated from all other types of calcium channels by their common sensitivity to 1,4-dihydropyridines. Thus, any one of these genes could be used to generate an L-type calcium channel for use in a cell-based assay to identify antagonists. These identified antagonists would bind to all of these L-type channels and thus would be useful in treating conditions related to any one of them.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at VANCOUVER, BC on 29 May 2001.

Terrance Snutch